Synopsis for Ph.D. Dissertation

Design and Evaluation of Microneedles for Management of Oral Cavity Diseases

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1. Introduction

The oral cavity, which includes a number of significant anatomical features, serves as the entrance to the digestive system. These consist of the lips, the soft palate (the muscular rear part), and the hard palate (the bony front part of the roof of the mouth). The front two-thirds of the tongue, the gingiva or gums, the buccal mucosa (the inner lining of the lips and cheeks), the floor of the mouth beneath the tongue, and the retromolartrigone—the region behind the wisdom teeth—are also included (1).

The crown and the root are the two primary components of a tooth's anatomy. Comprising a central pulp chamber, a supporting layer of dentine, and a hard outer coating of enamel, the crown is the visible portion of the oral cavity. The pulp tissue is essential to the health of teeth because it contains lymphatics, blood arteries, and nerves. The dentine and root canal are housed in the cementum, a bone-like substance that covers the root, which is lodged in the gum. The periodontal ligament, which joins the tooth to the surrounding alveolar bone, holds it firmly in place. Dental pulp stem cells are present in perivascular niches within the pulp tissue of permanent teeth and may be used in regenerative treatments (2).

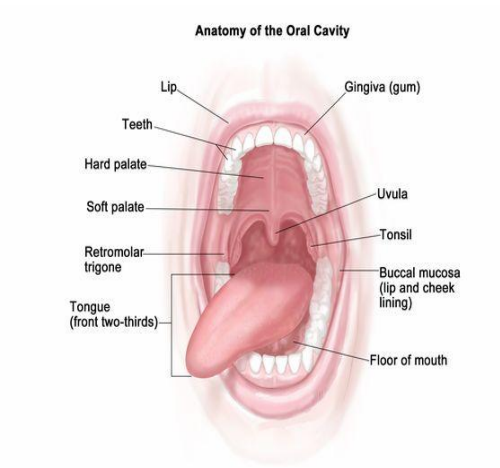

Fig 1: Oral Cavity(1)

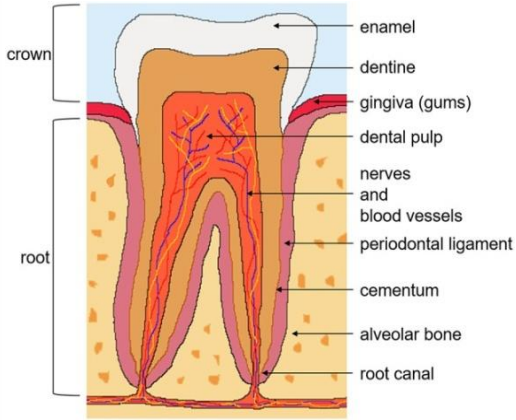

Fig 2: Tooth cavity(2)

Oral mucosa

The surface area of the oral mucosa is approximately 100 cm^2. The mucosal tissue of oral cavity can be categorized as-

1. The masticatory mucosa which covers the gingiva and hard palate, makesupto 25% of the overall oral mucosa.
2. The lining mucosa, which makes up 60% of the oral mucosa overall, covers the floor of the oral cavity, the lips, the cheeks, the soft palate, and the bottom portion of the tongue.
3. Tongue mucosa, the dorsum of the tongue contains 15% of the entire oral mucosa (2,3).

Oral cavity Diseases

Oral cavity diseases impact various parts of the mouth and can significantly reduce quality of life by compromising both dental and overall health. Common conditions include tooth decay, gum disease, and infections such as canker sores and dry mouth. In addition, more serious disorders like oral lichen planus, leukoplakia, oral thrush, and oral cancer may also develop. Some of these conditions can even signal underlying systemic health problems (4, 5). Oral infections are caused by a wide range of pathogens, including viruses, bacteria, and fungi. For example, human papillomavirus (HPV) can lead to oral papillomas (6), while other viruses such as Coxsackieviruses, Paramyxoviridae, and herpesviruses also contribute to oral diseases (7). Fungal infections from species like *Aspergillus*, *Cryptococcus*, and *Histoplasma* are common as well (8, 9). Additionally, bacterial species such as *Gemella*, *Granulicatella*, *Streptococcus*, and *Escherichia coli* are known to cause or exacerbate oral infections (10, 11). Conventional treatments for oral mucosal diseases include a range of solid, liquid, and semi-solid drug formulations, such as tablets, wafers, gels, ointments, and mouthwashes (12). However, these treatments often have limitations. The unique structure of the oral mucosa—with its mucous layers and salivary glands—poses challenges for effective drug absorption. Furthermore, medications administered orally often undergo first-pass metabolism in the liver or enzymatic breakdown in the gastrointestinal tract, resulting in low bioavailability. Frequent dosing is typically required, increasing the risk of systemic side effects. Mouthwashes and gels also tend to have short residence times, reducing the effectiveness of the active ingredients. Additionally, injection-based treatments can cause pain and discomfort, limiting patient compliance.

To overcome these limitations, innovative drug delivery methods such as microneedles are being explored. Microneedles offer a minimally invasive, efficient, and patient-friendly alternative to conventional drug delivery systems (13). These tiny needles—usually less than 1 mm in length—are designed to penetrate the outermost layer of the skin (stratum corneum)

without causing significant pain or tissue damage. By targeting specific areas in the mouth, microneedles can deliver drugs directly to affected tissues, allowing for controlled, sustained drug release and improved absorption. This targeted approach also reduces the required dosage, minimizing side effects and enhancing therapeutic outcomes.

Microneedle technology has shown promise across various medical fields, including dental care, diabetes management, vaccinations, and cosmetic procedures. Originating in the 1970s with a patent by Gerstel and Place at Alza Research, microneedles have since evolved into a versatile platform (14). They are capable of delivering a wide range of therapeutic agents, from small molecules and vaccines to proteins and even genetic materials like DNA and RNA (15). Furthermore, their biodegradable design reduces the risk of needle-stick injuries and medical waste, making them a sustainable and safe solution for modern healthcare.

Types of microneedles

The direct and regulated delivery of therapeutic drugs is made possible by microneedle technology, which may form small channels in the skin or mucosal tissues. Metals, polymers, silicon, and hydrogels are among the materials commonly used in the fabrication of these devices. Microneedles are fabricated by different method such as Micromolding, Elecrospinning, 3D printing (16, 17) etc.

Microneedles can be distinguished by their structure and operation as follows-

- *Solid microneedles*: Apply medication after pre-treating the skin.
- *Coated microneedles*: A substance is applied to the surface of the needle (18).
- *Hollow microneedles*: These less invasive needles deliver liquid medications to the skin similarly to conventional injections.
- *Dissolving microneedles***:**Composed of polymers laden with drugs that dissolve in the skin (19, 20).
- *Hydrogel-forming microneedles***:**These are biocompatibility, biodegradability, and prolonged drug release capabilities (21).

In the field of oral healthcare, microneedles in particular have shown a lot of promise. When these microneedles come into touch with tissue fluid, they are made to expand, forming microchannels that allow medications to diffuse straight into the underlying tissues. The components utilized to make microneedles include hyaluronic acid (HA), sodium alginate, pullulan, and chitosan derived from carbohydrates. Biocompatibility, non-toxicity, and safe degradation within the body are the reasons behind the selection of protein-based materials like silk fibroin, gelatin, and gelatin methacryloyl (GelMA) (21, 22) and synthetic

polymers like polyvinyl pyrrolidone, polyethylene glycol, polyvinyl alcohol, and polyacrylic acid (22).

The non-toxic nature of polymers is perfect for oral applications where the most important factors are safety and low irritation. Additionally, this work will investigate the possibility of using microneedle-based devices to provide a variety of therapeutic agents, such as anti-inflammatory, antibacterial, and anticancer medications including tannic acid (23), ferulic acid, piperine, gallic acid (24) and liguritenin, among others (25, 26) for the treatment of prevalent oral diseases. A number of important factors must be taken into account while designing and assessing microneedles for conditions affecting the oral cavity. The microneedles' mechanical strength must be adequate to pierce the mucosal barrier without shattering or causing undue discomfort. The therapeutic drugs' stability, release kinetics, and drug-loading capacity are additional important variables that affect how well a treatment works (27). In order to avoid negative reactions like inflammation, allergic reactions, or tissue damage, the biocompatibility and safety profile of the microneedle materials must also be carefully assessed.

2. **Literature review**

In the treatment of oral diseases, Microneedles (MNs) have shown promise as a focused, painless, and effective medication delivery method. According to studies, they can dissolve quickly, pass through the oral mucosa (120–500 µm), and release medications with regulated kinetics, including corticosteroids, antibiotics, anticancer medicines, and anesthetics. Strong anti-inflammatory, antibacterial, and regenerative qualities displayed by DMNs promote ulcer healing, increase the effectiveness of ALA-PDT, and increase patient compliance. The therapeutic potential of coated and biodegradable microneedles is increased, allowing for the delivery of cancer drugs and mucosal vaccination. Their adaptability in treating oral malignancies, leukoplakia, periodontitis, and ulcers is further demonstrated by innovations such as modular, wet-adhesive, and dual-release systems.

Sr.No	Drug	Microneedles	Highlight	Diseases
1)	Betamethasone-21-phosphate sodium, betamethasone 17,21-dipropionate	Dissolving microneedles	• Microneedles penetrated to a depth of 207 ± 3 µm, • Dissolving HA carrier releasing drug into the ulcer base within 3min • Cellular assays confirmed that BDP@HAMNs promote effective wound healing and strong anti-inflammatory properties	Oral ulcer (28)

2)	5-Aminolevulinic acid (ALA)	Dissolving microneedles	• The insertion depth was 500 µm, • morphology, strength, mucosal penetration and biocompatibility were seen. • The ALA-loaded microneedle patch offered an efficient delivery of drug • Increases clinical effectiveness of ALA-PDT in the treatment of oral leukoplakia (OLK).	Oral leukoplakia (29)
3)	Curcumin	Dissolving microneedles	• Microneedles enable precise, targeted delivery of curcumin and Mg^{2+} to the ulcer site. • controllable release mechanism for sustained therapeutic effects. • Significantly regulates inflammation, promotes cell migration and angiogenesis, and accelerates ulcer healing.	Oral ulcer (30)
4)	Antineoplastic drugs (photosensitizers)	Coated, dissolvable and biodegradables microneedles	• High efficiency, • convenience, • non-invasiveness • current research application of microneedles different cancer treatments is provided.	Oral cancer (16)
5)	Indocyanine green (ICG)	Dissolving microneedles patch, sodium carboxymethyl cellulose and sodium alginate	• DMN dissolved with in 30 sec in phosphate buffer and 30 min in the excised buccal mucosa. • Confocal microscopy studies revealed DMN penetration up to a depth of 300µm	Oral carcinoma (31)
6)	Sulforhodamine, ovalbumin, Two antigens	Coated microneedles	• This study provides a novel method using microneedles to induce systemic IgG and secretory IgA in saliva. versatile technique for oral mucosal vaccination	Systemic and mucosal immunity (32)
7)	Doxorubicin	Coated	• Prepare coated	Oral

		microneedles	microneedles for direct and minimally invasive intratumoral delivery of anti cancer drugs • Poly (lactic–co-glycolic) acid nanoparticles encapsulating doxorubicin were prepared and coated on in plane microneedles. • Buccal tissue up to a depth greater than 3mm	carcinomas (33)
8)	5-fluorouracil	Dissolving layered microneedles	• Sodium carboxymethyl cellulose, sodium alginate, and PEG 400 were used. • Micromolding technique. • Penetration depth 120μm. • Dissolved within 30s and 20 min. • Applying MN For 30 min resulted in an accumulation of 330ug/g in buccal tissue	Oral carcinoma (34)
9)	Green tea extracts	Dissolving Microneedles	• Antibacterial activity. • Covers up to ~50 mm^2 for broad application. • Controlled Degradation • Sustained Release: HAMN loaded with 70% GT maintained a continuous, higher release rate for 72 h	Wound healing (35)
10)	Antibiotics metronidazole	Dissolving microneedles	• MNs enable precise local drug delivery. • **Deep Penetration:** Reach gingival sulcus with minimal oral function impact. • Drugs encapsulated in PLGA shells for controlled delivery. • PLGA-TK-PEG MNs release metronidazole in high ROS environments for effective targeting.	Periodontal diseases treatment (36)
11)	Lidocaine	Dissolving microneedles	• Loaded with lidocaine hydrochloride for quick release. • PVA/CMC-Na with strong adhesion and water-	Local anaesthesia (37)

			absorbing properties. • Penetration Depth is 297 µm • Enhanced Convenience**,** Li-HAMNs show better topical anaesthesia than EMLA cream (1.2 mg lidocaine). • Li-HAMNs effective with just 0.5 mg lidocaine.	
12)	Curcumin analogue, AC17	Dissolving microneedles	• Curcumin Modification: Benzene ring and methylene group altered for enhanced activity**.** • AC17 Effect: Inhibits OSCC cell proliferation and induces cell cycle arrest. • Mechanism: Primarily affects apoptosis, cell cycle, and senescence pathways.	Oral squamous cell carcinoma (38)
13)	Triamcinolone	Wet adhesive microneedles	• High-effectiveness drug delivery system. • 0.071 N strength for mucosal penetration. • Silk fibroin and tannic acid (5:1 ratio) for max efficacy. • Long-Lasting Release • Strong Adhesion: Wet adhesion strength of 37.74 kPa for stability.	Oral submucous fibrosis (39)
14)	Antibiotics-tetracycline, Cytokines	Dissolving microneedles	• **Modular MN patch:** Enables controlled, multistage drug release. • **Dual delivery:** Antibiotics and cytokines target immune cells. • **Pro-regenerative effect:** Enhances tissue repair through local immunomodulation.	Periodontal tissue regeneration (40)
15)	Gallic acid	Dynamic hydrogel metal – organic framework	• **Synergistic effects with MOFs:** Enhance antibacterial functions. • Regulates immune response for better healing. • **Bone regeneration:** Promotes bone repair in	Bone regeneration in periodontitis (41)

			periodontitis.	
16)	Triamcinolone acetonide (TA)	Dissolving microneedles	• Designed for transmucosal delivery. • Mesoporouspolydopamine nanoparticles (MPDA) loaded with TA (TA@MPDA). • Sodium hyaluronic acid (HA) and Bletillastriata polysaccharide (BSP).	Oral mucositis (42)
17)	Human insulin, growth hormone	Dissolving microneedles	Increase medication adherence and facilitate the painless delivery	Buccal macromolecule delivery (43)
18)	Triamcinolone acetonide (TA) epidermal growth factor (EGF)	Dissolving microneedles	• Show strong anti-inflammatory, antibacterial, and tissue-healing effects. • Successfully promotes oral ulcer healing. •	Oral ulcer (44)
19)	Dexamethasone acetate, vitamin C and tetracaine hydrochloride	Dissolving microneedles	• **Enhanced effects**: Combines dexamethasone and vitamin C for better healing. • ***In vitro***: More effective than dexamethasone • **Cell growth**: Outperforms vitamin C in promoting cell proliferation. • ***In vivo***: Heals oral ulcers 2 days • Promising for recurrent oral ulcer treatment.	Oral ulcer (45)

3. Objectives

On review of literature it was observed that the microneedles (MNs), owing to their minimally invasive nature, potential for painless delivery, and ability to localize treatment, offer a promising alternative for targeted drug delivery in the oral cavity. However, their application in oral healthcare is still underexplored. Considering the growing need for

patient-friendly, efficient drug delivery systems, the present study was formulated with the following objectives-

1. To design and fabricate microneedles (MNs) suitable for localized drug delivery in the oral cavity.
2. To characterize the fabricated microneedles for mechanical properties, drug loading capacity, and *in vitro* drug release profiles.
3. To evaluate the biocompatibility and therapeutic effectiveness of the microneedles using appropriate *in vitro* and/or *in vivo* models relevant to oral diseases.

4. Plan of work

a) **Comprehensive Literature Review:**

Conduct an extensive review of existing research related to microneedle-based drug delivery systems, with a focus on their applications in oral diseases. This will help identify current knowledge gaps, formulation strategies, and suitable evaluation methods.

b) **Procurement of Materials:**

Procure necessary chemicals, polymers, and active pharmaceutical ingredients (APIs) required for the fabrication and evaluation of microneedle formulations.

c) **Fabrication of Microneedles:**

Develop microneedle patches using suitable techniques such as micromolding, 3D printing, or casting methods, depending on material compatibility and formulation requirements.

d) **Characterization of Microneedles:**

Evaluate the fabricated microneedles for critical parameters, including-Morphology (e.g., optical microscopy, SEM), Fourier Transform Infrared Spectroscopy (FTIR) ,Swelling behavior and adhesive performance, Mechanical strength, Drug loading efficiency and encapsulation efficiency, In vitro biocompatibility using suitable cell lines

e) ***In Vitro* Drug Release Studies:**

Investigate the drug release kinetics from the microneedles under controlled in vitro conditions using appropriate dissolution or diffusion systems (e.g., Franz diffusion cell).

f) ***In Vivo* Evaluation:**

Assess the therapeutic potential of the optimized microneedle formulation in animal models of oral diseases (such as oral ulcers or inflammation), following approval from

the Institutional Animal Ethics Committee (IAEC). Evaluate parameters such as healing time, tissue regeneration, and local drug retention.

5. Scope and Relevance:

Microneedle (MN) technology has been widely investigated in dermatology, transdermal drug delivery, and immunization due to its minimally invasive nature and capacity for controlled drug release. However, its application in treating oral diseases is still in early stages. Recent studies have demonstrated the successful use of MNs for localized delivery of corticosteroids, antibiotics, antifungals, and anticancer agents within the oral cavity, showing enhanced therapeutic effects, reduced systemic side effects, and improved wound healing. These outcomes highlight MNs as a promising alternative to conventional oral treatments. Despite these advantages, key challenges such as mucosal penetration, mechanical durability, material biocompatibility, and long-term safety remain major barriers to clinical translation. Further research is needed to optimize MN designs for the complex oral environment and broaden their therapeutic applications.

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